REMARKS

This is in response to the Office Action mailed on November 29, 2005, and the Decision on Pre-Appeal Brief mailed July 13, 2006.

Claims 24-29 have been added. Support of these claims can be found throughout the application and claims as originally filed. For example, the subject matter of claims 24, 25, 26 and 27 is supported by claims 2, 6, 8, 9 and 10. Claims 28 and 29 state that at least 90% and 95% are not killed, respectively. Support for the subject matter of claims 28 and 29 can be found throughout the specification, for example, at page 14, lines 28-33.

Claims 2 and 22 are amended. In particular, the term "peptide" has been deleted and replaced by "molecule," which is the term used in original claim 1. In addition, the terms "by irradiation" and "a lysosomotropic weak base" has been deleted from claims 2 and 22. Support for use of "molecule" instead of "peptide" can be found throughout the specification, for example, in claim 1 as originally filed.

Applicant submits that these changes have added no new matter to the application or claims.

§112 Rejections of the Claims

Enablement

Claims 2, 4, 6, 8-10 and 22 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Specifically, the Examiner alleges that the specification only enables use of antigen presenting cells and certain types of photosensitizing agents in the practice of the claimed method.

The test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987).

Claims 2 and 22 are directed to a method of expressing an antigenic molecule on the surface of a cell. While the Examiner asserts that "only certain antigen presenting cells are capable of presenting antigens and generating an immune response," Applicant reminds the Examiner that histocompatibility (MHC) molecules are glycoproteins at the surface of *essentially*

all vertebrate cells, and their normal function is to display antigens on *any cell* so that the antigens can be "seen" by T lymphocytes.

As evidence supporting the fact that all cells express MHC protein, Applicants submit pages 880-881 of James D. Watson et al., MOLECULAR BIOLOGY OF THE GENE, 4th ed. (The Benjamin/Cummings Publishing Company, Inc. 1987) in a Supplemental Information Disclosure Statement filed herewith. As indicated on page 880, MHC proteins are present on the surface of all cell types in the body and, for example, cytotoxic T cells are able to eliminate any cell types infected with virus because those cells display viral antigens. All that is needed is for the cell to express MHC (all cells do) and thereby display an antigen.

As evidence that the function of MHC molecules is to display antigens, Applicants submit an article entitled "Histocompatibility Molecules," downloaded from the web on Oct. 9, 2006 from http://home.comcast.net/~john.kimball1/BiologyPages/H/HLA.html (also submitted in the Supplemental Information Disclosure Statement filed herewith). As stated on page 3 of the "Histocompatibility Molecules" article and explained in more detail therein, "Histocompatibility molecules present antigens to T cells." Therefore, MHC molecules are expressed by all cells and the function of MHC molecules is to display antigens. Hence, any cell that expresses MHC can be used to display antigens.

If the MHC molecules displayed antigens on only some types of cells, or if only some types of cells could be recognized by cytotoxic T cells, then, for example, viral infections would run rampant throughout the body, infecting the cells that were incapable of viral antigen display and/or T cell recognition. Hosts with such impaired immune systems would likely die at an early age.

Accordingly, Applicant submits that any viable cell type can be used to express an antigen on its cell surface and requests withdrawal of this rejection with respect to the types of cells that can be used.

The Examiner has also asserted that the specification discloses only the actual use of $AlPcS_{2a}$ and $TPPS_{2a}$ photochemical internalization agents. "For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient." MPEP § 2164.02. Here, one of skill in the art would have no difficulty making and using any of the eight species recited in claims 2 and 22. The number of species is

not large (8), the skill in the art is high. The specification clearly describes how to use these species (see, e.g., Examples 1 and 2). The procedures for achieving photochemical internalization (mix antigenic molecules and photochemical internalization agent with cells and expose the mixture to light) are simple, and antigenic molecules (or fragments thereof) can readily be detected on the cell surface by numerous procedures, including by use of antibodies and/or by exposure to cytotoxic T cells (see Applicant's Examples). Applicant submits that the specification fully enables use of the claimed photosensitizing agents because one reasonably skilled in the art could make or use the invention from the disclosures in the patent without undue experimentation. Therefore, Applicant requests withdrawal of this rejection with respect to the photosensitizing agents.

The Examiner further alleges that specification does not show expression of any antigenic peptides on the surface of cells. However, the data of Example 2, particularly when combined with applicant's previous submissions, leave no doubt and actually compel a conclusion that the MART-1 peptide was expressed on the surface of the melanoma cells described therein.

As described in Example 2, FM3 melanoma cells were treated with the $AlPcS_{2a}$ photochemical internalization agent for 18 hours, then loaded with chromium and incubated with the MART-1 peptide for 5 hours. The chromium is taken up into the cells and used as a marker for cell lysis. After the chromium uptake and incubation with the MART-1 peptide, the cells are washed to remove residual peptide, chromium, etc. Then, the cells are exposed to light (as indicated in FIG. 3). The cells are then incubated for eighteen hours to allow internalization and display of the MART-1 peptide on the FM3 melanoma cells. After this incubation, the melanoma cells are exposed to cytotoxic T cells that were specific for the MART-1 peptide for four hours, and then the amount of chromium in the released into the medium was measured. FIG. 3 shows that the percent cytotoxicity increases with increasing time of light exposure. These results mean that two things must be happening: 1) the light promotes internalization and cell surface display; and 2) the cytotoxic T cells lyse cells that display the MART-1 peptide.

Please note that our earlier submissions, particularly, for example, the Declaration by Anders Høgst (dated Nov. 13, 2002), provide further results demonstrating that the present methods produce cell surface expression. For example, in his Declaration, Anders Høgst describes an experiment performed using the same procedures as those for Example 2, but with

and without the MART-1 peptide. The results are shown in Figure 1 of the Declaration and summarized by Anders Høgst as follows:

> It will be seen from this Figure [1] that virtually no CTL-dependent killing occurs without the MART-1 peptide, regardless of whether the cells are illuminated or not. Addition of the MART-1 peptide induces a small level of cell killing (about 3.5%) without illumination, but illumination increases the cell killing substantially (about 4-fold in this experiment). In view of the selectively of CTL for MART-1 peptide appropriately processed and presented on the surface of the cell, this illustrates that photochemical treatment results in MART-1 internalization, processing and presentation on the surface of the cells in a form such that immune effector T cells are able to recognize and eliminate those cells.

Declaration under Rule 132 at page 2, by Anders Høgst (Nov. 13, 2002). Therefore, the cytotoxic T cells (CTLs) only kill substantial numbers of cells when the MART-1 peptide is present and the cell-peptide mixture is illuminated with light. These results can only be explained by light-induced uptake and display of the MART-1 peptide.

These results are further confirmed by an understanding of the functions performed by cytotoxic T cells. As described in Watson et al. and "Histocompatibility Molecules," submitted herewith, cytotoxic T cell recognition and killing requires two things: MHC expression and a foreign antigen displayed on the surface of a cell. Without both the MHC and the displayed antigen, the cytotoxic T cell will not kill (e.g., lyse) the cell. Therefore, the melanoma cells of Example 2 *must* have displayed the MART-1 peptide (using MHC) or the MART-1-specific cytotoxic T cells would not have lysed these melanoma cells. No other conclusion is possible.

Accordingly, the Examiner's allegations are incorrect. Contrary to the Examiner's allegations, the application does show that the methods of the invention lead to display of antigenic molecules on the surface of cells (e.g. melanoma cells).

Moreover, the specification clearly does provide evidence not only of cell surface expression (via MHC machinery) but also of an immune response (cytotoxic T cell reaction against the surface-displayed MART-1 peptide).

Withdrawal of this rejection of claims 2, 4, 6, 8-10 and 22 under 35 U.S.C. § 112, first paragraph is respectfully requested.

Written Description

Claims 2, 4, 6, 8-10 and 22 was rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description. The Examiner alleges that Applicant was not in possession of a "lysomotropic weak base thereof" of a porphyrin, phthalocyanine, purpurin, chlorin, benzoporphyrin, naphthalocyanine, cationic dye, tetracycline at the time of filing. This rejection is respectfully traversed.

To satisfy the written description requirement, Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he was in possession of the invention, and that the invention, in that context, is whatever is now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991), and see M.P.E.P. § 2163.02.

The term "lysomotropic weak base thereof" has been removed from claims 2 and 22. Thus, claims 2 and 22 are directed to particular well-defined photosensitizing agents selected from the group consisting of a porphyrin, phthalocyanine, purpurin, chlorin, benzoporphyrin, naphthalocyanine, cationic dye, and tetracycline.

Applicant submits that one of skill in the art would understand that the inventors were in possession of the above listed eight well-defined photosensitizing agents at the time of filing the present application because these agents were explicitly listed in the specification at page 12, lines 25-31. One of skill in the art can have no doubt as to the possession of these agents by Applicants at the time of filing.

Withdrawal of this rejection of claims 2, 4, 6, 8-10 and 22 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

§102 Rejection of the Claims

Claims 2, 4, 6, 8-10 and 22 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by PCT Application Publication No. WO96/07432 by Berg. The Examiner alleges that WO96/07432 teaches a method of expressing an antigenic molecule on the surface of a viable cancer cell and while WO96/07432 does not expressly state that surface expression occurs, the Examiner alleges that cell surface expression would inherently result from the method steps employed.

As explained in more detail below, WO96/07432 fails to disclose all elements of Applicant's claims. In particular, at least two elements are missing from the WO96/07432 disclosure. First, WO96/07432 does not disclose "releasing said molecule into the cytosol of the cell, without killing the cell." And second, WO96/07432 does not disclose stimulation of an immune response either explicitly or implicitly.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ 2d 1913, 1920 (Fed. Cir. 1989). To constitute anticipation, the claimed subject matter must be identically disclosed in the prior art. *In re Arkley*, 172 U.S.P.Q. 524 at 526 (C.C.P.A. 1972). For anticipation, there must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the art. *Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 18 USPQ2d 101 (Fed. Cir. 1991). To overcome the defense of anticipation, "it is only necessary for the patentee to show some tangible difference between the invention and the prior art." *Del Mar Engineering Lab v. Physio-Tronics, Inc.*, 642 F.2d 1167, 1172, (9th Cir. 1981).

Moreover, an anticipation rejection that is based on inherency must be supported by factual and technical grounds establishing that the inherent feature must flow as a necessary conclusion, not simply a possible conclusion, from the teaching of the cited art. *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Int. 1990); *In re Oelrich*, 666 F.2d 578, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981).

WO96/07432 fails to disclose all elements of Applicant's claims because WO96/07432 does not disclose "releasing said molecule into the cytosol of the cell, without killing the cell." As explicitly stated in WO96/07432, the photodynamic treatment alone "kills 10-20% of the cells" (page 8, lines 20-21; Fig. 2; see also, page 3, lines 18-25), indicating that if the procedures of WO96/07432 were used to internalize non-toxic agents, those methods would be more destructive than those used by the present methods. In addition, all Examples of the WO96/07432 disclosure are focused on transfer of toxins into cellular cytosol for the express purpose of killing the cells. Therefore, WO96/07432 is limited to methods for introducing toxins

into cells and does not teach how to preserve cells so that they can live to express an antigenic molecule on the surface of a cell. In fact there is no disclosure whatsoever in WO96/07432 of antigenic molecules displayed on the surface of cells.

Thus, WO96/07432 fails to disclose all elements of Applicant's claims because WO96/07432 does not disclose "releasing said molecule into the cytosol of the cell, without killing the cell." In particular, as stated in new claims 28 and 29, at least 90% or 95% of the cells are not killed in the present procedures. Support for viable cells that are not killed by the present methods is present throughout the specification as filed, for example, at page 14, lines 28-33.

Moreover, WO96/07432 fails to disclose stimulation of an immune response either explicitly or implicitly, and the methods provided by WO96/07432 are not performed in a way that leads to antigen presentation and an immune response. WO96/07432 provides no disclosure that stimulation of an immune response can or should take place. For example, the terms "immune" and "immunological" appear nowhere in the WO96/07432 specification. Instead, WO96/07432 contemplates killing cells with cytotoxins. Therefore, because claim 2 is directed to stimulating an immune response and WO96/07432 provides no disclosure that such an immune response can or should take place, no anticipation of the present claims by WO96/07432 can be found.

The WO96/07432 specification does mention modifying the genetic make-up of a cell. However, the WO96/07432 specification but does not illustrate how to modify the genetic make-up of the cell and expressly teaches delivery into the cytosol for uptake into the endosomes and lysosomes (rather than the nucleus; see, e.g., WO96/07432 Abstract). Therefore, Applicants submit that such teachings are not relevant to the present invention. When read in its entirety, the WO96/07432 specification effectively teaches only transfer of cytotoxins into the cytoplasm of cells, and not expression of antigenic molecules on the surface of cells.

The Examiner has again questioned whether the present methods can lead to display of antigenic molecules on the surface of cells. However, as explained in the section on enablement, the data of Example 2 compel a conclusion that the MART-1 peptide was expressed on the surface of the melanoma cells described therein. Therefore, while the present invention

provides cell surface expression of antigens to stimulate an immune response, WO96/07432 provides no such disclosure.

Moreover, with respect to the Examiner's allegations regarding inherent anticipation, Applicant reminds the Examiner that an anticipation rejection that is based on inherency must be supported by factual and technical grounds establishing that the inherent feature must flow as a necessary conclusion, not simply a possible conclusion, from the teaching of the cited art. The Examiner appears to equating this standard with enablement. However, Applicant finds no reason to apply an enablement standard when the correct standard is the inherency standard.

Applicant submits that WO96/07432 does not provide factual grounds establishing that antigen presentation and stimulation of an immune response necessarily occurs. In particular, the specification discloses nothing about generating an immune response ("immune" and "immunological" appear nowhere) and each of the twelve examples recited in WO96/07432 utilizes a cytotoxin to kill the cells that internalize the cytotoxin. Thus, one of skill in the art could not conclude that an immune response necessarily occurs because WO96/07432 is silent on this issue and the WO96/07432 Examples all produce dead or dying cells. In addition, WO96/07432 uses methods that, even without the action of cytotoxins, kill 10-20% of the cells, whereas the present methods do not lead to such high levels of cell death. Hence, the present methods are distinct from those of WO96/07432 and no inherent anticipation can be found.

Applicant requests withdrawal of this rejection of claims 2, 4, 6, 8-10 and 22 under 35 U.S.C. § 102(b).

Conclusion

Applicants respectfully submit that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicants' attorney at (516) 795-6820 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

KRISTIAN BERG ET AL.

By their Representatives,

SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. Box 2938
Minneapolis, MN 55402
(516) 795-6820

Date October 13, 2006 By /Robin A. Chadwick/
Robin A. Chadwick
Reg. No. 36,477

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: ~~MS Amendment~~, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 13th day of October, 2006.

PATRICIA A. HULTMAN

Name

Signature